Gene Homology Explorer

Proposal

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2 Introduction

In the field of human genetic research, model organisms play a crucial role in helping to decipher functional mechanisms, disease mechanisms, variant impact, and many other aspects of genes[1]. Researchers in this field of study rely on previously published data in their organism of interest and also related organisms to discover as much information as possible. A geneticist studying the KRAS gene in humans might look for studies on related genes in mice or rats before designing experiments or looking for drug targets. These related genes are called *orthologs*. Orthologs are homologous genes that are the result of a speciation event[2]. In other words, a gene in one species that is directly, but possibly distantly, related to a gene in another species over an evolutionary time period. *Paralogs*, genes that are the result of a duplication event within a species, can also be used for this same purpose (Figure 1).

[1] needs citation

[2] Koonin EV. Orthologs, paralogs, and evolutionary genomics. Annu Rev Genet. 2005;39:309-38. doi: 10.1146/annurev.genet.39.073003.114725. PMID: 16285863.

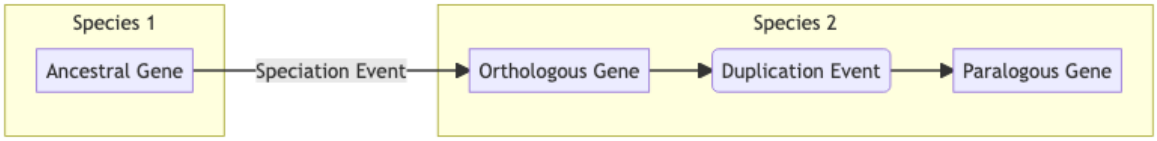

Figure 1: Origin of orthologous and paralogous genes.

2.1 Motivation

The exact definition of what constitutes an ortholgous or paralogous pair of genes has been an active area of study for decades[3]. Over this time, many orthology prediction algorithms have been developed, making it difficult for researchers to select one over the other. To address this issue a meta-orthology tool called DIOPT[4] was developed by the Perrimon lab at Harvard Medical School. DIOPT takes the approach of aggregating as many orthology and paralogy algorithm prediction results as possible and presenting all to the end user when a search for one or more genes is conducted. Each homologous pair of genes is scored according to the number of algorithms that have predicted their evolutionary relationship. The tool allows users to enter one or more genes and view results in a tabular format.

While useful, this functionality fails to convey the relationships between the genes being queried within a species, relationships to orthologous genes in other species, and paralogous genes in a visual manner. Herein, we propose the development of a network visualization tool that will allow researchers to explore these relationships, filter based on species, algorithm scores, or other attributes, and easily link out to primary source databases for additional information.

2.1.1 Related Work

To date, the presentation of results from DIOPT have been limited to tabular HTML results or downloadable tab separated files[5] [6]. Other resources that do offer a more visual presentation of homology data don't offer the meta analysis that DIOPT

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Herein, we propose the development of a network visualization tool that will allow researchers to explore these relationships, filter based on species, algorithm scores, or other attributes, and easily link out to primary source databases for additional information. Below are discussed details of the technical approach to accomplish this task and a project Road Map to outline key milestones and goals throughout the project duration.

3.1 Technical Approach

The overall technical approach for this project will be divided into 5 phases. Please refer to the Project Execution Roadmap for a more detailed breakdown with planned timelines.

1. Mockup design and stakeholder feedback
2. Data source acquisition and processing
3. Data warehouse creation

[3] needs citation

[4] Hu Y, Flockhart I, Vinayagam A, Bergwitz C, Berger B, Perrimon N, Mohr SE. An integrative approach to ortholog prediction for disease-focused and other functional studies. BMC Bioinformatics. 2011 Aug 31;12:357. doi: 10.1186/1471-2105-12-357. PMID: 21880147; PMCID: PMC3179972.

[5] Alliance of Genome Resources Consortium. Harmonizing model organism data in the Alliance of Genome Resources. Genetics. 2022 Apr 4;220(4):iyac022. doi: 10.1093/genetics/iyac022. PMID: 35380658; PMCID: PMC8982023.

[6] Gramates LS, Agapite J, Attrill H, Calvi BR, Crosby MA, Dos Santos G, Goodman JL, Goutte-Gattat D, Jenkins VK, Kaufman T, Larkin A, Matthews BB, Millburn G, Strelets VB; the FlyBase Consortium. FlyBase: a guided tour of highlighted features. Genetics. 2022 Apr 4;220(4):iyac035. doi: 10.1093/genetics/iyac035. PMID: 35266522; PMCID: PMC8982030.

4. Build network visualization
5. Network analysis implementation

3.1.1 Mockup Design and Stakeholder Feedback

The initial phase of this project will involve creating mockups of the planned user interface. This will help to solidify technical decisions for important aspects such as choice of a visualization tool, the underlying data system (JSON/TSV, SQL, NoSQL, or graph database). It may also help to identify additional data sources and network analysis algorithms that should be included. The mockups will then be shown to colleaugues or other domain experts to gather feedback on the intial designs. Given the tight timeline of the semester deadline there will likely only be time for 1 or 2 iterations with stakeholders.

3.1.2 Data Source Acquisition and Processing

Concurrently with mockups and stakeholder feedback, we will start the process of gathering the primary orthology and paralogy DIOPT data and performing initial processing and statistical analysis to assess any scaling issues that may arise later on. This will likely be done with Python scripts and automated as much as possible.

Data sources - DIOPT - Primary source of meta orthology and paralogy predictions. - Alliance of Genome Resources - Secondary source of gene functional and disease associations for all major model organisms. - Timetree of Life - Secondary source for evolutionary distance estimates between species.

The following model organism species will be included in the Homology Explorer tool.

Model Organism Species - Escherichia coli (E. coli) - Arabidopsis thaliana (Thale cress) - Schizosaccharomyces pombe (Fission yeast) - Saccharomyces cerevisiae (Yeast) - Caenorhabditis elegans (Worm) - Anopheles gambiae (Mosquito) - Drosophila melanogaster (Fly) - Danio rerio (Zebrafish) - Xenopus tropicalis (Western clawed frog) - Rattus norvegicus (Rat) - Mus musculus (Mouse) - Homo sapiens (Human)

The DIOPT dataset will give us our primary data for the Homology Explorer. Each gene in the dataset will represent a node in the network. The ortholog and paralog predictions will define the edges, with the DIOPT scores acting as weights on each edge. Additional information that may be added as attributes of the nodes and edges include functional gene ontology terms (GO), evolutionary distance estimates between species, and disease ontology (DO) associations.

3.1.3 Data Warehouse Creation

In order to power the network visualization a data system will need to be devised to support the final design features of the tool. The system will need to be able to serve data quickly and efficiently to the frontend, support basic search services, and possibly implement basic network analysis algorithms for performance reasons. We will evaluate the needs of the project and determine whether a NoSQL, SQL, or graph database is the best technology for the job.

3.1.4 Build Network Visualization

The Homology Explorer tool will utilize 3 possible existing web based network visualization tools as a starting point from which we will extend and implement the required features.

Network Visualization Tools - Cytoscape.js - Sigma - Vega

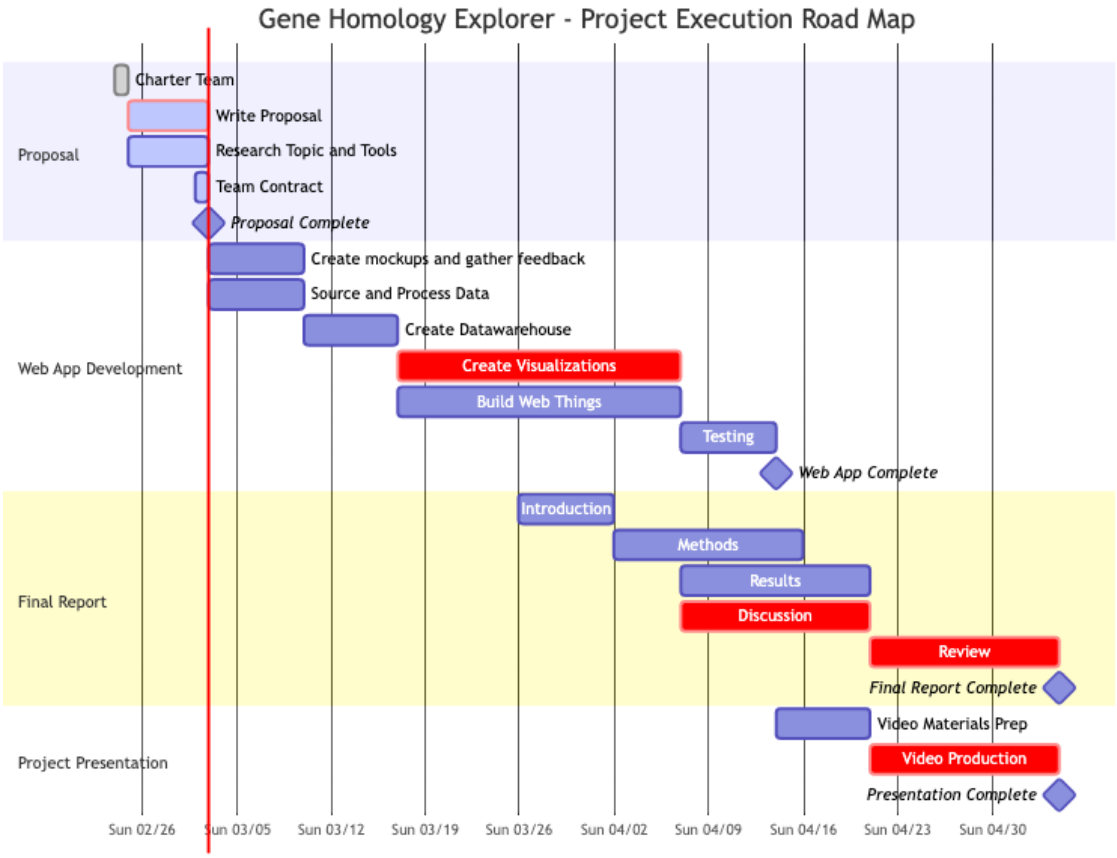
Web based network tools have limitations on the number of nodes and edges they can support before the tool becomes unusable. These limitations are mostly determined by the underlying technology used for painting the networks (SVG, Canvas, or WebGL). With these limitations in mind, each of these tools will need to be evaluated in the context of the finalized mockup and scale of the datasets before one is selected.

3.1.5 Network Analysis Implementation

Any thoughts here

Random thoughts - Shortest path between two genes utilizing the evolutionary distance estimates? - Centraility measures?

3.2 Project Execution Roadmap



4 Acknowledgments

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